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09/032,972	02/26/1998	ACHIM H. KROTZ	ISIS-2710	1518

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EXAMINER

CRANE, LAWRENCE E

ART UNIT	PAPER NUMBER
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1623

DATE MAILED: 07/30/2002

27

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. <b>09/032,972</b>	Applicant(s) <b>Krotz et al.</b>	
	Examiner <b>L. E. Crane</b>	Group Art Unit <b>1623</b>	

**- THE MAILING DATE of this communication appears on the cover sheet beneath the correspondence address -**

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ~~--3--~~ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be filed after six months from the date of this communication.
- If the prior for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 USC §133).

## Status

- ☒ Responsive to communication(s) filed on ~~-04/29/02 (amdt E)-~~.
- ☐ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

## Disposition of Claims

- ☒ Claims ~~--1-42--~~ are pending in the application. Claims ~~--1--~~ have been cancelled.
- Of the above claim(s) ~~--1--~~ is/are withdrawn from consideration.
- ☐ Claim(s) ~~--1--~~ is/are allowed.
- ☒ Claims ~~--1-42--~~ are rejected.
- ☐ Claim(s) ~~--1--~~ is/are objected to.
- ☐ Claim(s) ~~--1--~~ are subject to restriction or election requirement.

## Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The proposed drawing correction, filed on ~~--1--~~ are ☐ approved ☐ disapproved.
- ☐ The drawing(s) filed on ~~--1--~~ is/are objected to by the Examiner.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119(a)-(d)

- ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119 (a)-(d).
- ☐ All ☐ Some ☐ None of the CERTIFIED copies of the priority documents have been received.
- ☐ received in Application No. (Series Code/Serial Number) ~~--1--~~.
- ☐ received in the national stage application from the International Bureau (PCT Rule 17.2(a)).
- \* Certified copies not received: ~~--1--~~.

## Attachment(s)

- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). ~~--1--~~
- ☐ Notice of Reference(s) Cited, PTO-892
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Interview Summary, PTO-413
- ☐ Notice of Informal Patent Application, PTO-152
- ☒ Other: ~~-2nd copy of ref. UA-~~

U.S. Patent Trademark Office

## Office Action Summary

PTO-326 (Rev. 06/19/01)  
S. N. 09/032,972

Copy for ☒ FILE ☐ APPLICANT

Part of Paper No. **27**

Art Unit 1623

No claims have been cancelled, claim 42 have been amended, and no new claims have been added as per the amendment filed April 29, 2002.

Claims 1-42 remain in the case.

5 35 U.S.C. §101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title."

10 Claims 1-42 are rejected under 35 U.S.C. §101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. §101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd. App. ,1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149, 149 USPQ 475 (D.D.C. 15 1966).

Applicant is referred to the term "performed using an automated device" in the next to last line of claims 1, 21 and 42. Examiner suggests amending the noted term to read -- performed with an automated device --.

20 Applicant's arguments with respect to claims 1-42 have been considered but are moot in view of the new grounds of rejection.

Claims 1-41 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Art Unit 1623

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note  
5 the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such  
10 language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance,  
15 claims 1 and 21 at line 6 recite the broad recitation "comprising a protic acid in a solvent," and both claims at lines 7-9 also recite "the solvent being an aromatic solvent, ..." which is the narrower statement of the range/limitation.

Applicant's arguments with respect to claims 1-42 have been  
20 considered but are moot in view of the new grounds of rejection.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections made under this section in this Office action:

A person shall be entitled to a patent unless --

25 (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Art Unit 1623

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5 Claims 1-42 are rejected under 35 U.S.C. §102(a) as being anticipated by **Horn et al.** (PTO-892 ref. UA).

10 Applicant is referred to page 4844, columns 1-2, which immediately following the header "**Oligonucleotide synthesis**," discloses that "[o]ligonucleotides were synthesized by standard solid phase chemistry using 2-cyanoethyl phosphoramidite monomers." In the following paragraph this reference also discloses "the linear sequence" and in column 2 refers to "[t]he primary sequence was synthesized on an automated DNA synthesizer." And in the immediately following sentence this reference discloses "[t]he detritylation step used two 7 s pulses of 3% trichloroacetic acid (TCA) in toluene/CH<sub>2</sub>Cl<sub>2</sub> (1:1 v/v)." This  
15 limitation is directed to subject matter included with the term "comprising a protic acid in a solvent" found in step (c) of claims 1 and 21, and the parallel term "comprising dichloroacetic acid in toluene" in claim 42(fails to exclude the cited art). In light of the generic character of the remainder of claims 1, 21 and 42, all of the variations of the  
20 instant claimed process are deemed to have been anticipated by the noted reference.

Applicant's arguments with respect to claims 1-42 have been considered but are moot in view of the new grounds of rejection.

25 The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject

Art Unit 1623

matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made."

5        Claims 1-42 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Ravikumar '621** (PTO-892 ref. A) in view of **Caruthers et al. '679** (PTO-892 ref. G) and further in view of **Froehler et al. '076** (PTO-892 ref. H) and further in view of **Sproat et al.(I)** (PTO-892 ref. W), **Conway et al.** (PTO-892 ref. Y), **Atkinson et al.** (PTO-892 ref. Z), and **Sproat et al.(II)** (PTO-892 ref. RA).

10        The instant claims are directed to entirely conventional, 7 step oligonucleotide syntheses conducted using an automated device to execute steps 2-6 {aka steps b) through f)}, wherein the two variations from the prior art are i) the choice of solvent or solvent mixture present for deprotection step (c) and ii) the choice of substrate as a linear  
15        oligonucleotide as opposed to the branched oligonucleotide of the prior art.

20        **Ravikumar '621** (PTO-892 ref. A) discloses entirely conventional oligonucleotide synthesis wherein the solvent for the coupling step is acetonitrile in the examples and the P-protecting group varies from the conventional phosphorus-ester protecting group. At column 3 this reference refers to several different patents which disclose the solid phase synthesis of oligonucleotides including three **Caruthers et al.** patents now cited herein as PTO-892 references **I, J and K**. Each of  
25        these **Caruthers et al.** patents discloses the automation of the synthesis of oligonucleotides via process steps closely analogous to, if not identical with, the process steps claimed herein, the most detailed disclosure occurring in **Caruthers et al. '418** (PTO-892 ref. K). In the **Ravikumar '621** patent at column 10, lines 1-16, a generic disclosure of the process steps leading to an oligonucleotide is presented, including

Art Unit 1623

acid-mediated deprotection of the 5'-hydroxyl moiety of a solid-support-attached nucleoside. However, no disclosure of any preferred solvent for the required acid reagent is included. In the same column at line 50, the removal of 5'-hydroxyl protection by contact with acid from a solid-support-attached oligonucleotide is also taught without specifying any particular solvent. At column 14, lines 5-28, a more complete disclosure of possible 5'-hydroxyl protecting groups is provided along with a list of acids effective to deprotect, but no preferred solvents are listed. At column 18, lines 37-41, deprotection is accomplished by contact with a solution of dichloroacetic acid in dichloromethane, conditions repeated in subsequent experimental procedures. The choice of any particular deprotection solvent is therefore apparently a choice within the purview of the ordinary practitioner in view of this disclosure. This reference does not disclose the particular mixture of solvents selected for use in the instant claimed processes.

Caruthers et al. '679 (PTO-892 ref. G) at column 5, lines 10-14, teaches the use of "... any solvent which will dissolve the reactants ..." including a list of specific organic solvents for phosphoramidite-intermediate-based oligonucleotide synthesis. The context of this statement suggests that Caruthers was making reference to the coupling step. However, the same generic teaching appears to also apply to the deprotection step where four different solvent/reagent systems were disclosed by Caruthers as effective in the 5'-O-detritylation process:

- (1) see column 16, Table IV, footnote 1 (ZnBr<sub>2</sub> in nitromethane);
- (2) see column 16, Table V, footnote 1 (toluenesulfonic acid in chloroform:methanol (7:3));
- (3) see column 18, lines 26-28 (ZnBr<sub>2</sub> in nitromethane:methanol (19:1)); and
- (4) see column 19, lines 47-50 (80% acetic acid).

Art Unit 1623

This reference does not disclose the particular mixture of solvents selected for use in the instant claimed processes.

5        **Froehler et al. '076** (PTO-892 ref. H) discloses the use of H-phosphonate intermediates for the coupling step in the synthesis of oligonucleotides and phosphorothioate analogues thereof, including reference to the automated synthesis thereof using a "Biosearch Model 8600 DNA synthesizer" at column 9, lines 22-23. This reference also teaches the use of " ... an anhydrous organic solvent, preferably pyridine/acetonitrile ...," at column 5, lines 26-28. This "what ever works best" philosophy apparently also applies to the deprotection step; 10 see column 5, lines 38-47. The last line of this portion of column 5 is particularly instructive. After listing 3 (three) different deprotection reagent/solvent mixtures, Froehler suggests a very flexible "whatever works" approach by further stating that "[o]ther deprotection 15 procedures suitable for other known protecting groups will be apparent to the ordinary practitioner." This reference does not disclose the particular mixture of solvents selected for use in the instant claimed processes.

20        **Sproat et al.(I)** (PTO-892 ref. W) discloses at p. 52, (lines 2 and 18) that toluene is useful for the purification of synthetic nucleoside intermediates. Additionally, this reference discloses at pp. 64 (Protocol 17, step 3) and page 70 (Protocol 25, step 4) that benzene is a solvent for key oligonucleotide synthesis reagents and for nucleoside-3'-O-phosphoramidites, and may be used to co-evaporate triethylamine 25 therefrom.

**Conway et al.** (PTO-892 ref. Y) is directed to the chemical synthesis of labeled DNA and at p. 218, Section C, Subsection 2, discloses the specific use of toluene as an effective solvent for



Art Unit 1623

dissolution of pyridine-contaminated dinucleoside monophosphorothioate d[Cp(s)C] prior to co-evaporative removal of the pyridine/toluene mixture therefrom. The instant reference does not disclose that toluene is used in the coupling step required to make this compound.

Atkinson et al. (PTO-892 ref. Z) discloses at p. 43 in section (xvii), that toluene is useful to dissolve the 3'-O-phosphoramidites of 2'-deoxyadenosine, 2'-deoxycytidine, and 2'-deoxyuridine as the first step in a re-precipitation or recrystallization process. This reference also teaches at p. 76, section 7.5, "Variation in Procedures," although no specific teaching of the substitution of an aromatic solvent from other solvents used in oligonucleotide synthesis is present in this section. In section 8.7 at p. 80, "toluene" is listed as a reagent useful in the preparation of "Deoxyribonucleoside-derivatized supports." This reference at the noted locations does not disclose the particular set of solvents claimed herein as useful in the coupling step of an oligonucleotide synthesis.

Sproat et al.(II) (PTO-892 ref. RA).at p. 84, lines 10 and 9 from the end of the page, discloses that the "[p]urity of solvents and reagents is of the utmost importance as far as reliability and reproducibility of the [oligonucleotide synthetic] method are concerned." This reference also discloses at p. 93, section (xv), that a di-protected adenosine derivative may be effectively dissolved in toluene prior to evaporative solvent removal for the purpose of co-evaporating residues of pyridine therefrom (see also p. 96, section (vi) for a similar disclosure). Additionally, at p. 111, section 7.6, the listing of solvents useful in oligonucleotide synthesis includes both benzene and toluene. This reference at the noted locations does not disclose the particular set of

## Art Unit 1623

solvents claimed herein as useful in the coupling step of an oligonucleotide synthesis.

5 The teachings of the prior art Caruthers '679 and Froehler '076 references motivate the selection of practically any organic solvent or solvent mixtures which will dissolve the reactants and not otherwise interfere with the intended synthetic transformation. The first three references (A, G and H) and the additional Caruthers et al. patents cited by Ravikumar et al.'621 provide descriptions of conventional prior art processes for making oligonucleotides via phosphoramidite or H-  
10 phosphonate intermediates, including the 5'-O-deprotection process step and including details of how the process has been automated in H and by patents cited in A. The noted portions of the Caruthers '679 and Froehler '076 both teach that the choice of a particular solvent or solvent mixture is a variable clearly within the purview of the ordinary  
15 practitioner. The Sproat et al.(I) (W), Conway et al., Atkinson et al., and Sproat et al.(II)(RA) references are each generally directed to oligonucleotide synthesis thereby providing proper motivation to combine with the primary references. The secondary references provide disclosures that at least two different nucleoside-3'-O-phosphoramidites,  
20 at least one dinucleotide derivative, and some other nucleoside derivatives may be effectively dissolved in the aromatic hydrocarbon solvents benzene and/or toluene. These disclosures are deemed to provide factually specific motivations for the ordinary practitioner conducting routine experimentation to substitute toluene, benzene, or  
25 their closely related aromatic solvent relatives as substitutes for at least a portion of the solvents typically used during the deprotection step in oligonucleotide synthesis. And lastly, in light of the absence of any unexpected results, the choice of substrate (linear vs. branched oligonucleotide) is deemed to not be a basis for finding patentable

Art Unit 1623

distinction over the prior art of record. For these reasons the instant process claims are deemed to be lacking in any patentable distinction in view of the noted prior art.

5 Therefore, the instant claimed oligonucleotide processes would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made. \*\*\*

Applicant's arguments with respect to claims 1-42 have been considered but are moot in view of the new grounds of rejection.

10 Claims 1-42 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Horn et al.** (PTO-1449 ref. **CB**) in view of **Horn et al.** (PTO-892 ref. **UA**).

The subject matter of the instant claims is described in the previous rejection.

15 **Horn et al.(CB)** at page 6965, first complete paragraph (lines 19-28), discloses the use of dichloroacetic acid in toluene for the trityl deprotection step in the synthesis of branched oligonucleotides. Horn notes in particular that a higher than usual (for single deprotection) concentration of dichloroacetic acid effects rapid de-tritylation when multiple de-tritylations must be conducted simultaneously in the parallel  
20 extensions of separate oligonucleotide chains is required for the synthesis of multiply branched oligonucleotide "fork and comb" type probes.

25 **Horn et al.(UA)** at page 4844, columns 1-2 (following the header "**Oligonucleotide synthesis**"), discloses further details relevant to the application of a mixture comprising dichloroacetic acid and toluene to effect the de-tritylation of linear 5'-tritylated oligonucleotide precursors

Art Unit 1623

during the process of oligonucleotide chain extension. See particularly page 4844, column 2 at lines 6-8 and 25-28.

5 The prior disclosures of standard phosphoramidite-type oligonucleotide syntheses of either branched or linear oligonucleotides wherein the de-tritylation step relies on a mixture comprising dichloroacetic acid and toluene are deemed to be teachings which individually, or in combination, read on the instant claimed process. For this reasons the instant process claims are deemed to be lacking in any patentable distinction in view of the cited prior art.

10 Therefore, the instant claimed oligonucleotide processes would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Applicant's arguments with respect to claims 1-42 have been considered but are moot in view of the new grounds of rejection.

15 Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone numbers for the FAX machines operated by Group 1600 are (703) 308-4556 and 703-305-3592.

20 Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is 703-308-4639. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

Serial No. 09/032,972

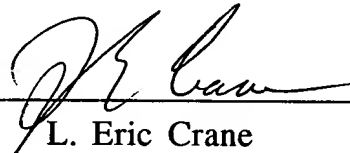
12

Art Unit 1623

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Johann Richter, can be reached at (703)-308-4532.

Any inquiry of a general nature or relating to the status of this  
5 application should be directed to the Group 1600 receptionist whose  
telephone number is 703-308-1235.

LECrane:lec  
07/29/02

10 

L. Eric Crane  
Patent Examiner  
Technology Center 1600